Eur J Vasc Endovasc Surg 14, 492–498 (1997)

Histopathological Features of *in situ* Vein Bypass Stenoses

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Objectives: *To analyse the histopathological features of* in situ *vein bypass stenoses.*
Materials and Methods: *Nineteen specimens of primary (n = 16) or recurrent (n = 3) vein graft stenoses obtained from 17 patients during surgical revision were prepared for light microscopy and immunohistochemical investigation. The median time interval from bypass surgery to stenosis excision was 5 months (range 2–52 months). Twenty-seven saphenous vein segments obtained from patients undergoing primary bypass surgery served as controls.*
Results: *Graft stenoses were characterised by moderate to severe intimal hyperplasia composed of actin positive but desmin negative cells, interspersed with areas of fibrosis. A single layer of factor VIII positive endothelial cells were identified on the luminal surface. The media, separated from the intima by a poorly defined elastic lamina, usually appeared normal or mildly hyperplastic and consisted of smooth muscle cells, which stained positive for actin as well as for desmin. The adventitia was composed of loose connective tissue in which lymphocytes, plasma cells and giant cells were occasionally seen. Atheromatous material was absent from intragraft lesions, but was observed in one specimen, which was harvested from a proximal anastomotic lesion. The majority of pre-bypass vein segments showed evidence of intimal thickening whereas medial hyperplasia was less common.*
Conclusions: In situ *vein bypass stenoses mainly consisted of intimal hyperplasia and varying degrees of fibrosis. Similar but less pronounced morphological changes were found in pre-bypass vein segments. The nature of the actin positive but desmin and factor VIII negative intima cells is uncertain, and further studies are needed to characterise this cell type.*

Key Words: Saphenous vein transplantation; Saphenous vein pathology; Patency; Vascular.

Introduction

Infrainguinal vein bypass surgery has become an established procedure for lower extremity revascularisation, providing long-term patency rates ranging from 60–90%.[1-3] Early reconstruction failures occurring within the first postoperative month have been attributed to inadequate patient selection or technical problems related to the operation. Late failures occuring more than 1–2 years after surgery mainly result from progression of atherosclerosis in the in- and outflow arteries as well as in the graft. Failures in the intermediate period account for the majority of all failures and result from graft-related stenoses.[4-10] The pathogenesis of vein graft stenoses has been extensively studied *in vitro* and in animal models.[11-15] The initiating event is assumed to be intraoperative injury of the saphenous vein, which in combination with humoral factors and endothelial dysfunction leads to an accelerated healing response resulting in progressive intimal thickening and consequently luminal narrowing.[10,11,15,16] A detailed immunohistochemical analysis of the cellular components of vein bypass stenoses in humans, however, has not previously been carried out. With the aim of gaining further insight into the pathogenesis of vein graft failure, we analysed the composition of surgically corrected *in situ* vein bypass stenoses.

Materials and Methods

Nineteen tissue specimens from 17 patients were harvested during surgical revision of strictured *in situ* vein grafts at the Department of Vascular Surgery, Rigshospitalet, Copenhagen between March 1992 and July 1995. The median age of the 12 males and five females was 73 years (range 39–82 years). Seven (41%) patients had diabetes, four (24%) were hypertensive and 14 (82%) were current or previous smokers. Stenosis characteristics were determined angiographically.

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Four (21%) stenoses were located at the proximal anastomosis, 10 (53%) in the body of the graft and five (26%) at the distal anastomosis. The luminal diameter reduction was 50–79% in eight (42%) and ≥80% in 11 (58%) cases. Stenosis length was <1 cm in five (26%) cases, 1.0–4.9 cm in 10 (53%) cases and ≥5 cm in four (21%) cases.

Sixteen specimens were retrieved from primary lesions, whereas three were from recurrent or residual lesions after previous percutaneous transluminal angioplasty ($n=2$) or surgical revision ($n=1$). The median time from the bypass operation to re-intervention was 5 months (range 2–52 months). Fourteen (74%) lesions were excised in total and a biopsy was obtained in the other five (26%) cases. All biopsies were taken at right angles to the vessel, included the entire vessel wall and typically measured 2 × 3 × 6 mm. Pre-bypass vein segments obtained from the distal end of the saphenous vein in 27 patients (19 males and eight females, median age 68 years (range 40–85 years)) undergoing primary vein bypass surgery served as controls. The specimens were fixed in formalin and embedded in paraffin. Sections were cut from the most severely stenosed part of the specimens and stained with hematoxylin-eosin and Verhoeffs staining method for elastin. Immunohistochemical staining for actin, desmin, vimentin and factor VIII was used to identify the cellular components. The histological changes were semi-quantified in four grades: grade I represented no or minimal hyperplasia, grade II mild hyperplasia, grade III moderate hyperplasia and grade IV severe hyperplasia, as previously described by Milroy *et al.*[17]

Immunohistochemical techniques

The antibodies used were: Monoclonal mouse anti-human α-smooth muscle actin (DAKOpatts M 0851, diluted 1:100), monoclonal mouse anti-swine desmin (DAKOpatts M 724, diluted 1:100), monoclonal mouse anti-swine vimentin (DAKOpatts M 725, diluted 1:400) and rabbit anti-human von Willebrand factor (factor VIII, DAKOpatts A 082, diluted 1:200).

For the monoclonal anti-bodies an avidin-biotin three stage method was used (DAKOpatts K 0355). For the polyclonal antibody a three stage peroxidase-antiperoxidase technique was used (DAKOpatts Z 0113). As chromogen, 3-amino-9-ethylcarbazole (AEC) was used.

The antibody against *actin* reacts with the α-smooth muscle isoform of actin. The antibody does not react with actin from fibroblasts, striated muscle or myocardium. The antibody reacts with smooth muscle cells of vessels and different parenchymes. The antibody against *desmin* reacts with 53 kD intermediate filament protein desmin in muscle cells. The antibody does not appear to recognise other filament proteins. In normal tissue it reacts with striated and smooth muscle cells. The labelling is confined to the Z bands in skeletal and cardiac muscle. The antibody against *vimentin* reacts with vimentin, the 57 kD intermediate filament protein present in cells of mesenchymal origin. Cells positive to the antibody include lymphoid cells, endothelial cells, fibroblasts and smooth muscle. Some cells co-express another intermediate filament protein besides vimentin. An example of this is vascular smooth muscle cells, which co-express desmin and vimentin. The antibody against *factor VIII* was raised against von Willebrand factor in human plasma, and reacts with endothelial cells in the vessels.

Statistics

The frequency of histological changes in vein graft stenoses and in pre-bypass vein segments was compared by Fisher's exact test.

Results

Primary intermediate (1–24 months postoperative) stenoses (n = *14*)

In two of the vein biopsies the layers were poorly defined and grading of the histological changes was not possible. The remaining 12 specimens were characterised by moderate ($n=4$) to severe ($n=8$) intimal hyperplasia (Table 1) (Fig. 1). In all instances a single layer of factor VIII positive endothelial cells lined the luminal surface (Fig. 2b) and several layers of actin positive but desmin negative cells were located beneath the endothelium (Fig. 2c and 2d). Variable degrees of fibrotic changes were found in the thickened intima. The border between intima and media was only vaguely defined, because the inner elastic laminae were split and partly disrupted. Thickening of the medial muscle layers was common, but generally less pronounced than the intimal thickening (Table 1). The media was composed of smooth muscle cells, which were positive for both actin and desmin (Fig. 2c and 2d). The adventitia consisted of loose connective tissue in which lymphocytes, plasma cells or giant cells occasionally were present. Scattered vimentin positive fibroblasts were found in all layers. No lipid, haemorrhage, thrombus or calcification was identified.

Table 1. Histological changes in 12 (#) infrainguinal vein bypass stenoses revised between 1 and 24 months postoperatively.

	Intima	Media		
		Inner longitudinal muscle layer	Circular muscle layer	Outer longitudinal muscle layer
No or minimal hyperplasia (Grade I)	0	3	6	9
Mild hyperplasia (Grade II)	0	9	4	3
Moderate hyperplasia (Grade III)	4	0	2	0
Severe hyperplasia (Grade IV)	8	0	0	0
p-value	0.02	0.006	0.2	0.9

p-values indicate results of Fisher's exact test when comparing the frequency of grade II–IV changes in vein graft stenoses and in pre-bypass vein segments: # = in two specimens with poorly defined layers the histological changes could not be classified.

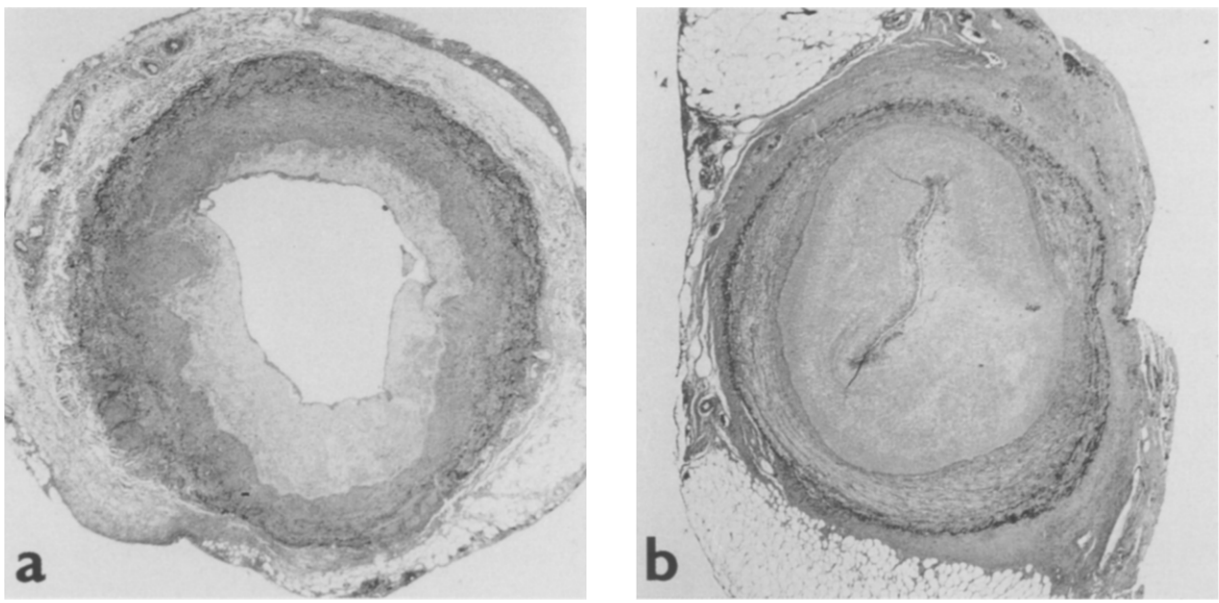

Fig. 1. Stenosed vein grafts. (a) Vein graft stenosis (Verhoeff stain, magnification ×12); (b) severe hyperplasia and high grade stenosis (Verhoeff stain, magnification ×12).

Primary late (>24 months postoperative) stenoses (n = 2)

A specimen obtained from a stenosis located at the proximal anastomosis 33 months postoperatively was composed of rather acellular connective tissue in addition to atheromatous material and calcification. The cells were predominantly actin positive, a few stained for vimentin, but there was no reaction in the desmin staining. An intragraft stenosis retrieved 52 months after surgery consisted of intimal hyperplasia which was markedly fibrotic.

Recurrent/residual stenoses (n = 3)

The recurrent lesions were characterised by intimal hyperplasia consisting of actin positive cells and were lined by a layer of factor VIII positive endothelial cells on the luminal surface. The media was composed of actin and desmin positive smooth muscle cells. Lymphocytes and giant cells were present in adventitia in two patients. A fresh thrombus was noted in one patient, which had been subjected to unsuccessful balloon angioplasty 4 days prior to the stenosis excision.

Pre-bypass vein segments serving as controls (n = 27)

In 16 (59%) patients the pre-bypass vein segments showed evidence of mild ($n = 11$), moderate ($n = 3$) or severe ($n = 2$) intimal thickening (Fig. 3), consisting of actin positive but desmin negative cells (Table 2). The luminal surface was lined by a single layer of factor VIII positive endothelial cells and the outermost limit of intima was marked by a poorly defined elastic lamina. One specimen contained atheromatous material and calcification. The three muscular layers in

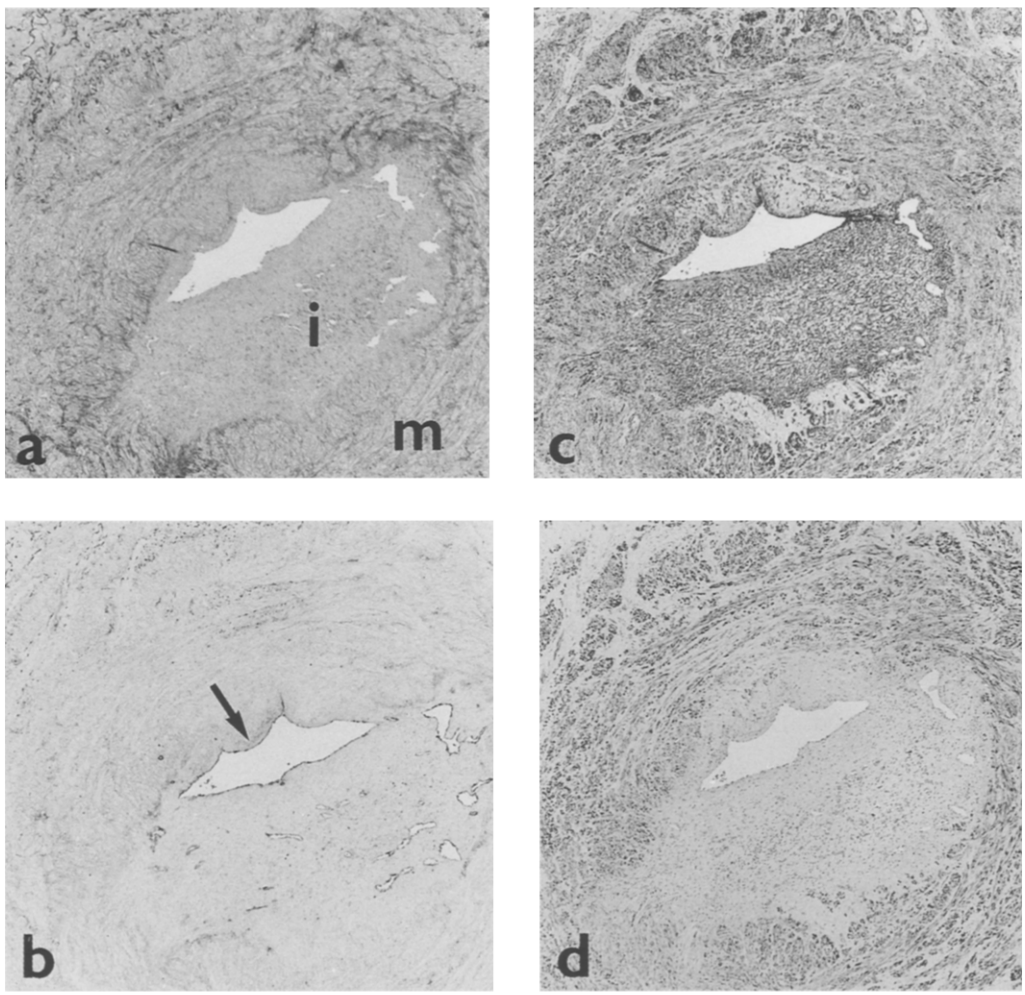

Fig. 2. Vein graft stenosis with severe intimal hyperplasia, magnification ×30. (a) Verhoeff stain (i=intima, m=media); (b) immunohistochemical staining for factor VIII (arrow indicates endothelial cells); (c) immunohistochemical staining for actin; (d) immunohistochemical staining for desmin.

the media appeared normal or mildly thickened in the majority of cases (Table 2). The medial cells stained positive for actin as well as for desmin. The adventitia was composed of loose connective tissue in which disrupted elastic laminae were identified.

Discussion

Early studies addressing vein bypass histopathology were based on grafts excised following thrombosis or at autopsy, usually several months after bypass surgery.[7,18] These studies have provided valuable insight into the morphological response to arterialisation of the saphenous vein. With the introduction of routine bypass surveillance, analysis of focal stenoses obtained during elective bypass revision has also become possible. However, as the number of surgical revisions is limited, these latter studies only comprise a total of 27 specimens, and furthermore immunohistochemistry has rarely been used[19–21] (Table 3). The present study confirmed previous observations that vein graft stenoses predominantly consist of a rather cellular intimal or subintimal hyperplasia. A detailed immunohistochemical analysis revealed that the medial cells, which contained both contractile actin filaments and intermediate desmin filaments, were true smooth muscle cells. On the other hand, the unexpected finding that the intima cells contained actin but not desmin filaments questions the nature of these cells. The absence of factor VIII activity suggests that they do not originate from endothelial cells, whereas the absence of desmin suggests that if they originate from smooth muscle cells they must have undergone structural alteration. Further studies, preferably using a combination of immunohistochemistry and electron micro-

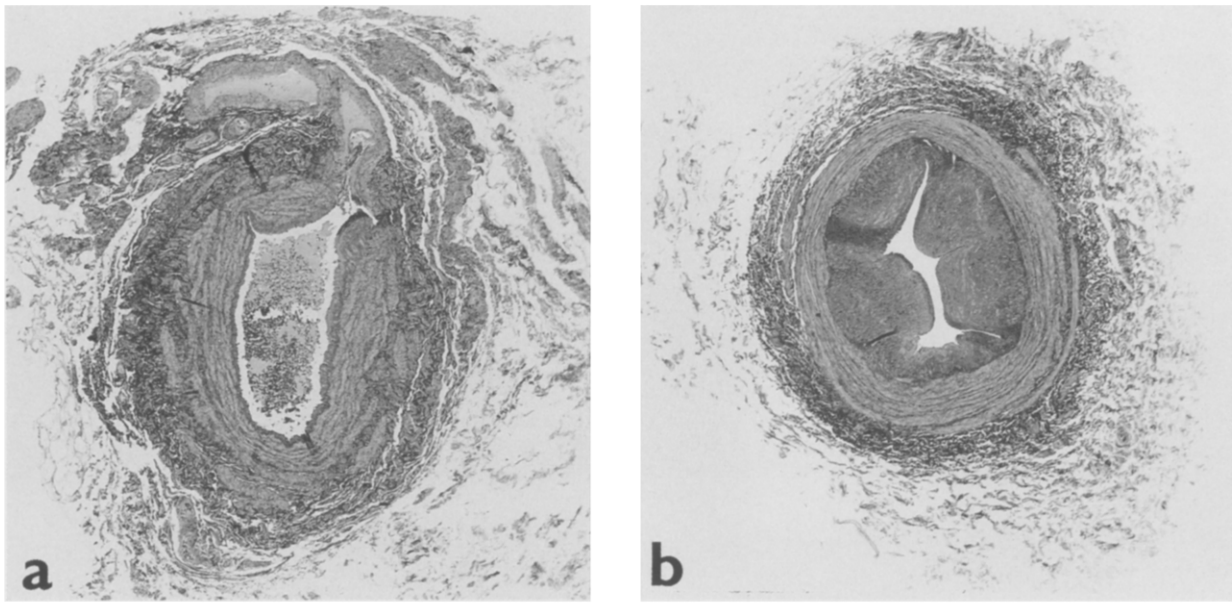

Fig. 3. Pre-bypass vein segments. (a) Normal vein (Verhoeff stain, magnification ×30); (b) vein with intimal hyperplasia (Verhoeff stain, magnification ×30).

Table 2. Histological changes in 27 control vein segments obtained from patients undergoing primary infrainguinal vein bypass surgery.

	Intima	Media		
		Inner longitudinal muscle layer	Circular muscle layer	Outer longitudinal muscle layer
No or minimal hyperplasia (Grade I)	11	21	17	22
Mild hyperplasia (Grade II)	11	5	8	5
Moderate hyperplasia (Grade III)	3	0	1	0
Severe hyperplasia (Grade IV)	2	1	1	0

Table 3. Reported studies on histopathology of failing infrainguinal vein bypasses.

Study	Number of grafts	Time interval from surgery to tissue harvest months (range)	Histological methods	Main findings
Szilagyi *et al.* (1973)	21 *	20 (6–96)	LM	Atherosclerosis ($n=8$) Fibrosis ($n=7$) IH ($n=4$) "Normal" grafts ($n=2$)
Sottiurai *et al.* (1983)	11 *	(11–43)	LM+EM	IH ($n=6$) "Normal" grafts ($n=5$)
Marin *et al.* (1993)	8 §	6 (3–13)	LM	IH
Sayers *et al.* (1993)	4 §	24 (7–60)	LM Anti-actin	IH
Marin *et al.* (1993)	15 §	Not reported	LM	Cellular IH ($n=4$) Mixed fibrous and cellular IH ($n=11$)
Present study (1997)	19 §	5 (2–52)	LM Anti-actin Anti-desmin Anti-vimentin	Mixed fibrous and cellular IH ($n=18$) Atherosclerosis ($n=1$)

LM = light microscopy; EM = electron microscopy; anti-actin = immunohistochemical staining for actin; anti-desmin = immunohistochemical staining for desmin; anti-vimentin = immunohistochemical staining for vimentin; IH = intimal hyperplasia; * = specimens harvested from thrombosed grafts or at autopsy; § = specimens harvested from stenoses during surgical revision.

scopy are needed to characterise and establish the origin of the hyperplastic intimal cells. Corroborating our findings, desmin positive cells are exclusively[22] or mainly[23] present in the media in coronary vein bypass stenoses.

Five other studies on the histopathology of peripheral vein bypass stenoses in humans have been published (Table 3) and a desmin stain was not used in any of these. In the original series of 21 specimens obtained during autopsy or surgical revision Szilagyi *et al.*[7] found intimal hyperplasia in four cases, fibrosis in seven and atherosclerotic changes in eight. The remaining two cases were non-diseased grafts. The median time interval from bypass grafting to tissue harvest was 12 months for lesions composed of intimal hyperplasia, 19 months for the fibrotic stenoses and 59 months for the atherosclerotic changes. Using light microscopy Marin *et al.*[19] analysed 15 midgraft vein graft stenoses prior to and after balloon dilatation. These lesions consisted of intimal hyperplasia of varying cellularity and fibrosis. No information about the age of the stenoses was given. In another study Marin and associates[20] examined biopsies of eight stenoses revised 3–13 months postoperatively and found spindle- or stellate-shaped cells dispersed within a dense fibrous tissue matrix. Thickened intimas of a similar appearance were identified in pre-bypass vein segments in six of these eight cases. In a recent publication Sayers *et al.*[21] described the histological structure of two *in situ* and two reversed vein graft stenoses corrected surgically a median of 24 months postoperatively. Intimal hyperplasia composed of smooth muscle cells, with or without superadded thrombus, was the dominant finding. Sottiurai *et al.*[18] studied 11 distal anastomoses harvested from thrombosed vein grafts at reoperation or amputation. The time interval from graft insertion to revision ranged from 11–43 months. In five of the graft segments there were no pathological findings, but in the other six, intimal hyperplasia was identified at the heel and toe of the anastomosis. Transmission electron microscopy revealed that the intima cells were smooth muscle cells, some of which showed evidence of degenerative changes whereas others were transformed into myofibroblasts, characterised by fewer myofilaments, large amounts of rough endoplasmatic reticulum and numerous Golgi complexes. These myofibroblasts are assumed to be involved in the synthesis of extracellular matrix and collagen fibres.[18,24]

In the present study lipid and calcification were identified in only one specimen, which originated from a proximal anastomosis lesion harvested 33 months postoperatively and therefore may represent progression of the inflow atherosclerosis rather than being a true graft lesion. In accord with Szilagyi's[7] observations atherosclerotic material and calcification are frequently found in older coronary vein bypass stenoses.[22] It therefore seems likely that the initial cellular intimal hyperplasia gradually becomes more fibrotic and eventually undergoes atherosclerotic degradation, similar to the structural alterations occurring in arterial stenoses with time.

In accordance with previous reports[20,25,26] we found that saphenous vein segments obtained prior to bypass grafting showed evidence of intimal hyperplasia of the exact same composition as graft stenoses. These pre-existing vein changes are assumed to adversely influence bypass patency,[20] possibly by forming a nidus for thrombosis and continued intimal hyperplasia.[27] Recently, however, the role of vein morphology in the development of graft stenoses has been questioned[28] and further prospective studies are necessary to clarify this issue.

The histopathological changes after vascular injury have been extensively studied *in vitro* and *in vivo*. Endothelial denudation induces lymphocyte infiltration, platelet aggregation and mural thrombus formation. Minor injuries are re-endothelialised within days by ingrowth of viable endothelial cells originating from the edges or from the adjacent in- or outflow artery. More extensive damage of the intima and medial cells leads to migration of smooth muscle cells from the media through disrupted elastic laminae to the intima, and results in subsequent proliferation in the intima.[15] Several growth factors including fibroblast factor (FGF), platelet derived growth factor (PDGF) and interleukin 1-α released from the damaged intimal cells and from thrombocytes may stimulate this process.[11,29,30]

The histological features of vein bypass stenoses in humans closely resemble the structural changes induced by vascular injury and thus support the hypothesis of a causal relationship between intraoperative vein graft injury and postoperative development of stenoses.[10,11,15] The traumatic events initiating the intimal hyperplasia have not been identified. Though surgical preparation of the saphenous vein leads to morphological and functional endothelial injury,[16] a prospective study[31] failed to show any correlation between clamp sites, sidebranches or valve cusps and the postoperative of stenoses. Compliance mismatch or geometric deformations due to suture lines,[32] perianastomotic turbulence[14] or altered haemodynamic conditions following arterialisation[10] may be of pathophysiological significance.

In conclusion, vein graft stenoses are characterised by intimal hyperplasia interspersed with areas of fibrosis. Further *in vivo* studies are needed to characterise

the nature of the intima cells and to elucidate the pathogenesis of vein graft stenoses in humans.

Acknowledgements

This study was financially supported by the Danish Heart Foundation. Jan Lauritzen, technician is thanked for doing all the immunohistochemical staining.

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Accepted 28 May 1997